GNAS gene

GNAS complex locus

Normal Function

The *GNAS* gene provides instructions for making one component, the stimulatory alpha subunit, of a protein complex called a guanine nucleotide-binding protein (G protein). Each G protein is composed of three proteins called the alpha, beta, and gamma subunits.

In a process called signal transduction, G proteins trigger a complex network of signaling pathways that ultimately influence many cell functions by regulating the activity of hormones. The G protein made with the subunit produced from the *GNAS* gene helps stimulate the activity of an enzyme called adenylate cyclase. This enzyme is involved in controlling the production of several hormones that help regulate the activity of endocrine glands such as the thyroid, pituitary gland, ovaries and testes (gonads), and adrenal glands. Adenylate cyclase is also believed to play a key role in signaling pathways that help regulate the development of bone (osteogenesis). In this way, the enzyme helps prevent the body from producing bone tissue in the wrong place (ectopic bone).

Health Conditions Related to Genetic Changes

McCune-Albright syndrome

At least three *GNAS* gene mutations have been identified in people with McCune-Albright syndrome, a disorder that affects the bones, skin, and several hormone-producing (endocrine) tissues. These mutations result in an abnormal version of the G protein that causes the adenylate cyclase enzyme to be constantly turned on (constitutively activated). Constitutive activation of the adenylate cyclase enzyme leads to over-production of several hormones, resulting in the signs and symptoms of McCune-Albright syndrome.

McCune-Albright syndrome is not inherited. The gene mutation that causes this disorder is described as somatic. Instead of being passed from parent to child, somatic mutations are acquired during a person's lifetime and are present only in certain cells. McCune-Albright syndrome is caused by a random mutation in the *GNAS* gene that occurs very early in development. As a result, some of the body's cells have a normal version of the *GNAS* gene, while other cells have the mutated version. This phenomenon is called mosaicism. The severity of this disorder and its specific features depend on the number and location of cells that have the mutated *GNAS* gene.

primary macronodular adrenal hyperplasia

At least two mutations in the *GNAS* gene have been identified in people with primary macronodular adrenal hyperplasia (PMAH), a disorder that causes multiple lumps (nodules) to form in the adrenal glands, which are small hormone-producing glands located on top of each kidney. These nodules cause adrenal gland enlargement (hyperplasia) and result in production of higher-than-normal levels of the hormone cortisol. Cortisol normally helps maintain blood sugar levels, protects the body from physical stress, and suppresses inflammation. Increased cortisol levels can lead to weight gain in the face and upper body, fragile skin, bone loss, fatigue, and other health problems, which often occur in people with PMAH.

The *GNAS* gene mutations that cause PMAH are believed to result in an overactive G protein. Research suggests that the overactive G protein may increase levels of adenylate cyclase, which results in the overproduction of another compound called cyclic AMP (cAMP). An excess of cAMP may trigger abnormal cell growth and lead to the adrenal nodules characteristic of PMAH.

As in McCune-Albright syndrome, the *GNAS* gene mutations that cause PMAH are somatic mutations that are believed to occur early in embryonic development. Cells with the mutated *GNAS* gene can be found in both adrenal glands.

progressive osseous heteroplasia

At least 14 *GNAS* gene mutations have been identified in people with progressive osseous heteroplasia. People normally inherit one copy of each gene from their mother and one copy from their father. For most genes, both copies are active, or "turned on," in all cells. For a small subset of genes, however, only one of the two gene copies is active. For some of these genes, only the copy inherited from a person's father (the paternal copy) is active, while for other genes, only the copy inherited from a person's mother (the maternal copy) is active. These differences in gene activation based on the gene's parent of origin are caused by a phenomenon called genomic imprinting.

The *GNAS* gene has a complex genomic imprinting pattern. In some parts of the body the maternal copy of the gene is active, while in others the paternal copy is active. Progressive osseous heteroplasia is caused by certain mutations that affect the paternal copy of the gene. These mutations disrupt the function of the G protein and impair its ability to regulate osteogenesis. Impaired regulation of osteogenesis results in the ectopic production of bony tissue in the skin and muscles seen in progressive osseous heteroplasia.

other disorders

Mutations in the *GNAS* gene also cause Albright hereditary osteodystrophy (AHO), which is characterized by short stature, obesity, unusually short fingers and toes (brachydactyly), ectopic development of bony tissue under the skin, and other

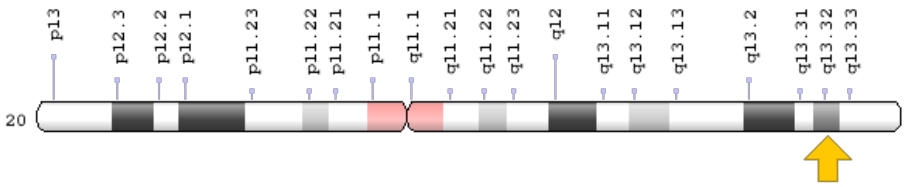
skeletal abnormalities. When a mutation that causes AHO is inherited from a person's mother, the affected individual will usually have AHO accompanied by a resistance to multiple hormones (a condition called pseudohypoparathyroidism type Ia, or PHPIa). A paternally-inherited mutation can result in AHO without endocrine problems; this form of the condition is called pseudopseudohypoparathyroidism (PPHP).

Somatic mutations in the *GNAS* gene have been found in tumors of the endocrine glands and in fibrous lesions (dysplasia) that can occur in bones. These mutations are believed to result in an overactive G protein, which triggers abnormal cell growth. Because the cells with mutations are not as widespread in the body as in McCune-Albright syndrome (described above), the abnormal growth is confined to a particular gland or fibrous lesion.

Chromosomal Location

Cytogenetic Location: 20q13.32, which is the long (q) arm of chromosome 20 at position 13.32

Molecular Location: base pairs 58,839,681 to 58,911,196 on chromosome 20 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- adenylate cyclase-stimulating G alpha protein
- ADENYLATE CYCLASE STIMULATORY PROTEIN, ALPHA SUBUNIT
- AHO
- C20orf45
- dJ309F20.1.1
- dJ806M20.3.3
- GNAS1
- GNAS1_HUMAN
- GNASXL

- GPSA
- Gs, ALPHA SUBUNIT
- GSA
- GSP
- guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1
- guanine nucleotide regulatory protein
- MGC33735
- NESP
- NESP55
- NEUROENDOCRINE SECRETORY PROTEIN 55
- PHP1A
- PHP1B
- POH
- SCG6
- secretogranin VI
- SgVI
- STIMULATORY G PROTEIN

Additional Information & Resources

GeneReviews

- Fibrous Dysplasia/McCune-Albright Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK274564

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28GNAS%5BTIAB%5D%29+OR+%28GNAS+complex+locus%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- GNAS COMPLEX LOCUS
  http://omim.org/entry/139320
- PSEUDOHYPOPARATHYROIDISM, TYPE IA
  http://omim.org/entry/103580
- PSEUDOPSEUDOHYPOPARATHYROIDISM
  http://omim.org/entry/612463

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GNASID40727ch20q13.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=GNAS%5Bgene%5D
- HGNC Gene Family: Granins
  http://www.genenames.org/cgi-bin/genefamilies/set/925
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=4392
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2778
- UniProt: ALEX_HUMAN
  http://www.uniprot.org/uniprot/P84996
- UniProt: GNAS1_HUMAN
  http://www.uniprot.org/uniprot/Q5JWF2
- UniProt: GNAS2_HUMAN
  http://www.uniprot.org/uniprot/P63092
- UniProt: GNAS3_HUMAN
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